

REMARKS

Status of Application

Upon entry of the requested Amendment, above, pending claims are 19-34 and 38. Applicant amended claims 19, 21, 23-25, and 27-34 to incorporate limitations of cancelled claim 16 on which they depend. Applicant added new claim 38, which is derived from cancelled claim 37, now dependent from elected claims. No new subject matter was added by these amendments. Applicant requests entry of the above amendments

Applicant does not affirm the election as stated by Examiner in the office Action mailed September 1, 2006. Applicant believes that the telephonic agreement was to elect Group I, claims 1-37, limited to oxycodone and the pentacyclic compounds of original claim 18.

To clarify and advance this prosecution, Applicant hereby elects Group I for examination, and specifically, claims 19-34 as currently amended and new claim 38. These claims encompass and are limited to oxycodone prodrugs and pharmaceutical formulations comprising one or more oxycodone prodrugs.

Applicant reserves the right to prosecute any withdrawn, canceled, or non-elected claims and/or subject matter, including the pentacyclic compounds of original claim 18, in separate applications.

Applicant requests reconsideration and allowance of claims 19-34 and 38.

35 U.S.C. § 102 Rejections

Examiner rejected claims 1-18 and 35-37 under 35 U.S.C. § 102 as being anticipated. Applicant has withdrawn claims 1-18 and 35-37, which obviates these rejections.

35 U.S.C. § 103 Rejections

Examiner rejected claims 19-34 as obvious over Piccariello (WO 03/072046). Examiner stated that "[t]he oxycodone esters of [the] instant claims differ from the oxycodone esters prepared by Piccariello ... by having [a] different group or moiety attached to the ester function (O(CO)C) of the oxycodone molecule." Examiner further stated that Piccariello teaches that "this group or moiety can be any chemical substance that can be attached to the controlled substance in a manner that renders it pharmacologically inactive." Examiner concluded, without

further explanation, that it would have been obvious to prepare Applicant's compounds "without affecting their utility of lowering abuse potential of oxycodone."

Applicant respectfully submits that the compounds and compositions of claims 19-34 and 37 as amended are not obvious over Piccariello. Examiner has not supplied a *prima facie* case of obviousness of claims 19-34 and 37 as amended. To show a *prima facie* case of obviousness Examiner must show that there is a reasonable expectation of success of modifying the compounds of Piccariello to obtain Applicant's oxycodone compounds. Examiner is required to point specific portions of the Piccariello reference which establish a reasonable expectation of success and provide the motivation for a person of ordinary skill in the art to make such modifications. Examiner has not provided the specific teachings required to support Examiner's conclusion of obviousness of Applicant's compounds and compositions.

In general, it is not possible to predict how changes in structure of an opiate would modify its duration of pharmacological action or its pharmacokinetic parameters. For example, heroin, the diacetyl ester derivative of the controlled substance morphine, is active and more abuse prone than morphine itself. In light of this unpredictability, Examiner must outline specific teachings in the prior art which show that Applicant's particular oxycodone compounds would have been known to reduce abuse potential.

The portion of the Piccariello reference relied upon by Examiner (paragraphs 42-44, page 10) provides only a generic description in the broadest terms that any controlled substance can be bound to a "carrier having a free carboxy and/or amine terminal and/or side chain groups other than the location of attachment for the active agent." This description encompasses a vast and unlimited number of compounds which provides no guidance whatsoever that would have led to Applicant's oxycodone compounds.

This portion of Piccariello relied upon by Examiner also states that the carrier or chemical moiety may be "any chemical substance that can be attached to the controlled substance in a manner that renders it pharmacologically inactive." This general statement is clearly an overly broad description of an unlimited number of compounds that does not point in any way to Applicant's oxycodone compounds. This general statement is also objectively false because many highly toxic chemical substances would not be expected to be useful as the carrier

or chemical moiety for a controlled substance, even though they could be attached to a controlled substance.

Applicant submits that Piccariello teaches that the preferred chemical moiety is an amino acid or oligopeptide (Piccariello, paragraphs 43, 45 and 49-59). The examples in Piccariello include Glu(O^tBu), Lys(Boc), Leu, Gly, and Ser(O^tBu) directly attached to an oxycodone (Piccariello, Figure 5).

Applicant therefore submits that Piccariello does not provide any teaching that would have led to the compounds of Applicant's claims 25-28, 30, and 32-34 as amended which do not encompass an amino acid directly attached to an oxycodone.

Applicant further submits that Piccariello does not provide any teaching that would have led to the compounds of Applicant's claims 19-22 as amended which encompass a polyethyleneglycol polymer component attached to an oxycodone, and Applicant's claims 23-24 as amended which encompass a polyethyleneglycol polymer component attached to an oxycodone as well as optional polymer moieties. Piccariello expressly excludes in a preferred embodiment "a amino acid copolymerized with a non-amino acid substitute such as PVP, a poly(alkylene oxide) amino acid copolymer." (Piccariello, paragraph 68, page 16). Further, Piccariello clearly prefers only "naturally occurring amino acids." (Piccariello, paragraph 43, page 10). Thus, Piccariello expressly teaches away from Applicant's claims 19-24 which encompass a polyethyleneglycol polymer component.

Applicant further submits that Piccariello fails to provide any teaching that would have led to the compounds of Applicant's invention, *inter alia*, of claims 21, 22, 27 and 31. As Examiner noted, Piccariello teaches only oxycodone esters. Piccariello actually teaches away from Applicant's claimed invention in that Piccariello's compounds are designed to have susceptibility to enzymatic cleavage, while the compounds of the claimed invention are enzyme-resistant: the result is that the claimed compounds have a much longer lifetime in the circulation. Piccariello fails to teach how to achieve a desired duration of the drug in blood equal to that or greater than that seen with typical controlled release formulations of un-conjugated drugs.

Moreover, Piccariello teaches away from those compounds of Applicant's claims 19-20, 23-24, and 31 which may include a Glu directly attached to an oxycodone. Piccariello states that

"Glu-Oxycodone, however, is not sufficiently stable to warrant consideration as an anti-abuse product." (Piccariello, paragraph 99, page 30).

In conclusion, Piccariello does not supply the teaching to show a reasonable expectation of success of modifying the compounds of Piccariello to obtain Applicant's oxycodone compounds. Examiner has not provided specific evidence to establish the expectation and motivation for a person of ordinary skill in the art to make such modifications. To the contrary, Piccariello expressly points away from Applicant's oxycodone compounds and compositions of claims 19-34 and 37 as amended.

In addition, Examiner's argument that Applicant's compounds and compositions are obvious in view of any chemical substance, or any amino acid, or any peptide attached to an oxycodone that would affect its narcotic activity is clearly an argument that the combination is "obvious to try." Examiner is respectfully reminded that "obvious to try" is an improper standard under 35 U.S.C. § 103. *See, e.g., In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988). Where the prior art gives no direction as to which of many possible choices is likely to be successful, no reasonable expectation of success exists which could motivate a person of ordinary skill in the art to achieve the claimed invention.

Applicant believes that claims 19-34 and 37 are in condition for allowance and respectfully requests reconsideration. Should there remain any unresolved issue that would require an adverse action, it is respectfully requested that the Examiner telephone Applicant's attorney so that such issue may be resolved as expeditiously as possible.

Should the U.S. Patent and Trademark Office determine that additional fees are due or that a refund is owed for this application, the Commissioner is hereby authorized and requested to charge the required fee and/or credit the refund owed to our Deposit Account No. 502769.

Respectfully Submitted,
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